UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460
OFFICE OF PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

April 3, 2008

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

MEMORANDUM

SUBJECT: OXYFLUORFEN. Review of Non-Guideline Hepatic Peroxisome Proliferation Study.

PC Code: 111601
MRID No.: 46373101
Petition No.: None
Assessment Type: None
TXR No.: 0053039

DP Barcode: D312067
Registration No.: None
Regulatory Action: None
Reregistration Case No.: None

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Executive Summary

Attached is a review for a non-guideline hepatic peroxisome proliferation study with oxyfluorfen. Following is the citation.

Stott, W.T., S.J. Day, B.L. Yano, *et al.* (2003) Oxyfluorfen: evaluation of hepatic peroxisome proliferation in CD-1 mice. Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI. Laboratory Project Study ID.: 021109, April 17, 2003. MRID 46373101. Unpublished.

DATA EVALUATION RECORD

OXYFLUORFEN

Study Type: Non-guideline Hepatic Peroxisome Proliferation Study in Mice

Work Assignment No. 3-1-83 (MRID 46373101)

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Disclaimer

This Data Evaluation Record may have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel.

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Template version 11/01

DATA EVALUATION RECORD

TXR #: 0053039

STUDY TYPE: Non-guideline Hepatic Peroxisome Proliferation Study in Mice (Dietary)

PC CODE: 111601 **DP BARCODE:** D312067

TEST MATERIAL (PURITY): Oxyfluorfen (99.87% a.i.)

SYNONYMS: 2-Chloro-1-(3-ethoxy-4-nitrophenoxy)-4-(trifluoromethyl)benzene; GOAL, RH-32915

CITATION: Stott, W.T., S.J. Day, B.L. Yano, *et al.* (2003) Oxyfluorfen: evaluation of hepatic peroxisome proliferation in CD-1 mice. Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI. Laboratory Project Study ID.: 021109, April 17, 2003. MRID 46373101. Unpublished.

SPONSOR: Dow AgroSciences LLC, 9330 Zionsville Road, Indianapolis, IN

EXECUTIVE SUMMARY - In a non-guideline oral toxicity study (MRID 46373101), Oxyfluorfen (99.87%; Lot No.: 2-4400) was administered in the diet to male CD-1 mice (10/dose/interval) at nominal concentrations of 0, 40, 200, or 800 ppm (equivalent to 0, 5.8, 28.5, and 120.3 mg/kg/day) for 7 or 28 days. Additionally, 10 mice treated at 800 ppm for 28 days and then maintained on untreated diet for 28 days were compared to 10 controls maintained over the same period. The stated purpose of this study was to determine the potential of oxyfluorfen to induce peroxisome proliferation in male mice.

No treatment-related effects were observed on mortality, clinical signs, body weight, body weight gain, or food consumption. There was no evidence of an increase in number of peroxisomes in the 800 ppm group in comparison to controls.

At 200 ppm (a tumorigenic dosage), minor increases were observed in liver weights. Only a minimal increase (not statistically significant [NS]) in acyl-CoA oxidase activity was noted at 200 ppm (incr 55%). On Day 28, the hepatocellular S-phase DNA synthesis labeling index (%) was increased (NS) in the centrilobular (incr 143%), midzonal (incr 73%), and periportal (incr

75%) regions. Histological hepatic lesions on day 28 included: (i) increased incidences of slight centrilobular/midzonal hepatocyte hypertrophy (6 vs 3); (ii) very slight to moderate centrilobular/midzonal hepatocyte vacuolization consistent with fatty change (5 vs 0).

At 800 ppm, absolute and relative to body liver weights were increased ($p<=0.05$) at Days 7 and 28 (incr 25-28%). Hepatocellular S-phase DNA synthesis labeling index was increased at Days 7 (incr 116-128%) and 28 (incr 778-1022%) in each hepatic region (centrilobular, midzonal, and periportal). Specific activity (nm/min/mg protein) of acyl-CoA oxidase was increased ($p<=0.05$) by 395% by Day 28. Histological hepatic lesions noted on Day 28 included: (i) increased incidences of slight centrilobular/midzonal hepatocyte hypertrophy (10 vs 3); (ii) very slight to moderate centrilobular/midzonal hepatocyte vacuolization consistent with fatty change (10 vs 0); (iii) very slight to slight multifocal centrilobular/midzonal hepatocyte necrosis (9 vs 0); (iv) very slight subacute to chronic multifocal inflammation (6 vs 0); (v) very slight multifocal hepatocyte karyomegaly (4 vs 0); (vi) very slight multifocal centrilobular/midzonal hepatocyte mitotic alteration (5 vs 0); and (vii) very slight multifocal sinusoid centrilobular/midzonal pigment laden macrophages (4 vs 0).

After the recovery period, all findings in the 800 ppm group were completely or partially restored to normal, except slight centrilobular/midzonal hepatocyte hypertrophy (10/10 treated vs 5/10 controls) and very slight multifocal hepatocyte karyomegaly (8/10 treated vs 0/10 controls).

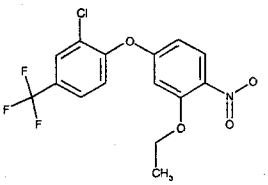
This study is classified **acceptable/non-guideline**.

COMPLIANCE - Signed and dated GLP Compliance, Data Confidentiality, Quality Assurance, and Flagging statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: Oxyfluorfen

Description:	Solid
Lot #:	2-4400
Purity (w/w):	99.87%
Stability of compound:	Stable for 11 days (room temperature assumed)
CAS #:	42874-03-3
Structure:	

2. Vehicle - Diet

3. Test animals

Species:	Mouse (males only)
Strain:	CD-1
Age and group mean weight at Day 1:	11-12 weeks; 34.3-34.8g males
Source:	Charles River Laboratories Inc. (Portage, MI)
Housing:	Individually in suspended stainless steel cages with wire-mesh floors
Diet:	LabDiet® Certified Rodent Diet #5002 (PMI Nutrition International, St. Louis, MO), *ad libitum*
Water:	Tap water, *ad libitum*
Environmental conditions	
Temperature:	21.5-22.2°C
Humidity:	46.9-54.9%
Air changes:	12-15 times/hour
Photoperiod:	12 hours light/12 hours dark
Acclimation period:	at least 1 week

B. STUDY DESIGN

1. Purpose: The stated purpose of this study was to determine the potential of oxyfluorfen to induce peroxisome proliferation in male mice.

2. In life dates - Start: approximately 8/21/02 End: 10/16/02

3. Animal assignment - The mice were randomly assigned, stratified by weight, to the test groups shown in Table 1.

Table 1. Study design [a]

Test Group	Dose (ppm)	Dose (mg/kg/day)	# of Males/Interval [b]
Control	0	0	10 [c]
Low	40	5.8	10
Mid	200	28.5	10
High	800	120.3	10 [c]

a Data were obtained on pages 19 (Text Table 3) and 26 of MRID 46373101.
b 10 mice were sacrificed after 7 days and another 10 after 28 days of treatment.
c An additional 10 mice were treated at 800 ppm for 28 days and then were maintained on untreated diet for 28 days. These mice were compared to an additional 10 controls maintained over the same period.

4. Dose-selection rationale - The Sponsor stated that in CD-1 mice, 200 ppm dietary formulations resulted in liver tumors in an oncogenicity study and that 200 and 800 ppm dietary formulations resulted in dose-related increases in liver weights and hepatic histopathologic change, including hypertrophy, in a 90-day subchronic study. The 40 ppm group was expected to have findings that were similar to controls.

5. Treatment preparation, administration, and analysis - Dietary formulations were prepared weekly by serially diluting a concentrated test material-feed mixture (premix) with ground feed to achieve the desired concentrations. All dietary formulation analyses were conducted prior to animal treatment. Stability was tested for 11 days (temperature not reported) in 0.004% and 4% formulations. Homogeneity (top, bottom) was evaluated in the 40 and 800 ppm formulations (triplicate samples). Concentration analyses were performed on all dietary formulations.

Results: **Homogeneity (% RSD):** 2.6% (800 ppm); 7.2% (40 ppm)

Stability (% initial) 102-111%

Concentration (range as % of the nominal concentration): 90.5-95.3%

The analytical data indicated that the mixing procedure was adequate and that the variation between nominal and actual dosage to the animals was acceptable.

6. Statistics - Body weights, food consumption, organ weights, enzyme data, and S-phase DNA synthesis data were first analyzed with Bartlett's test (α=0.01). Data with homogeneous variance were subjected to analysis of variance (α=0.05) followed by Dunnett's test (α=0.05). Data with heterogenous variance were subjected to non-parametric analysis of variance (α=0.05; Hollander and Wolfe, 1973) followed by Wilcoxon Rank-Sum test with a Bonferroni correction (α=0.05). Statistical outliers were identified by a sequential test (α=0.02; Grubbs, 1969). Outliers were routinely excluded from the statistical analysis of food consumption, but were excluded from other analyses only for documented, scientifically sound reasons.

C. METHODS

1. Observations - Animals were inspected twice daily for morbidity, mortality, and availability of food and water. Clinical examinations were conducted at least once a day. Detailed clinical observations were conducted on all animals pre-exposure and at least weekly. These observations included evaluation of skin, fur, mucous membranes, respiration, nervous system function (including tremors and convulsions), swelling, masses, and animal behavior.

2. Body weight - All animals were weighed prior to treatment, weekly during the study, and at sacrifice. Body weight gains were also calculated.

3. Food consumption - Food consumption was reported weekly as g/mouse/day. Compound intake values (mg/kg/day) were calculated using the food consumption, body weight, and nominal dietary concentration data.

4. Sacrifice and pathology - At study termination, all animals were sacrificed without fasting. Animals were anesthetized by the inhalation of CO_2, weighed, and euthanized by decapitation. The liver was removed, weighed, sectioned, and processed according to the requirements of subsequent analytical procedures. Additionally, a sample of duodenum was collected and fixed in formalin to serve as a positive control for 5-bromo-2'-deoxyuridine (BrdU) uptake.

5. Hepatic tissue examination

5.a. S-phase DNA synthesis - Animals were continuously infused with BrdU via implanted osmotic mini-pumps (Model 2001, Alzet Corporation, Pal0 Alto, CA) during the first week of dosing, the fourth week of dosing, or the fourth week of the recovery period. The pumps were implanted approximately 7 days prior to necropsy. Liver sections were preserved in neutral, phosphate-buffered 10% formalin. Levels of hepatic S-phase DNA synthesis were determined using the immunohistochemistry method outlined by Eldridge *et al.* (1990). Liver samples were processed by standard techniques, and BrdU containing nuclei were immunohistochemically identified. A small section of the duodenum from each mouse was also processed to serve as a control for confirming the systemic availability of BrdU. The numbers of BrdU labeled and unlabeled nuclei were counted from the centrilobular, midzonal, and periportal regions of the liver lobules. A labeling index was calculated as the percentage of immunohistochemically-stained nuclei to total nuclei (approximately 1000 nuclei/zone).

5.b. Peroxisome quantitation - Livers from 5 control and 4 high dose mice were examined by electron microscopy. Liver sections diced in 1 mm cubes were preserved in phosphate-buffered solution of 2% glutaraldehyde - 2% paraformaldehyde. Following fixation for at least 2 hours, samples were post-fixed in diaminobenzidine and subsequently dehydrated according to standard procedures. Stained tissue from 5 mice in the control and high-dose groups were embedded in epon/araldite epoxy resin. Central vein regions were selected, and thin sections (60-90 millimicrons thick) were cut. These sections were picked up on copper grids, air dried, and stained with uranyl acetate and lead citrate. Mounted tissue was digitally photographed using a transmission electron microscope.

5.c. Acyl-CoA oxidase (ACO) assay - Liver sections from the 28-day and recovery groups were placed in foil, flash frozen in liquid nitrogen, and stored at -80°C until further processing. Frozen samples were thawed on ice, homogenized in 10% sucrose (w/w) with 3 mM imidazole (pH 7.4), and centrifuged. Supernatants were stored at -80°C until assayed. Total homogenate protein for each sample was determined by the Pierce BCA™ method. ACO activity was measured as the lauryl-CoA-dependent production of hydrogen peroxide. This was quantitated by measuring the oxidation of 4-hydroxyphenylacetic acid to a fluorescent product at 405 nm wavelength after excitation at 320 nm in a horseradish peroxidase-coupled assay (Poosch and Yamazaki, 1986). Measurements were performed in triplicate.

5.d. Histologic examination - Liver sections adjacent to those used in the S-phase DNA synthesis evaluations were preserved in neutral, phosphate-buffered 10% formalin. The sections were processed routinely, stained with hematoxylin and eosin, and examined microscopically. Lesions were graded as very slight, slight, moderate, or severe.

II. RESULTS

A. OBSERVATIONS

1. Clinical signs of toxicity - No treatment-related clinical signs were observed.

2. Mortality - All mice survived until the scheduled sacrifice.

B. BODY WEIGHT AND WEIGHT GAIN - No treatment-related adverse effect on body weights and body weight gains were observed. Body weights of the 800 ppm group were increased over the controls during the recovery period, but this was considered an incidental effect. There was an increase (statistical analysis not performed) in body weight gain with dose at Weeks 1, 2, and 4 (↑4-64%); however, this increase was not considered adverse as only minor differences were observed in terminal body weights (↓2% after treatment and ↑8% after recovery).

C. FOOD CONSUMPTION - No treatment-related effect was observed on food consumption. In the 800 ppm group, incidental, minor increases ($p \leq 0.05$) in food consumption were observed during Days 14-21 (↑8%) and Days 42-49 (↑9%; recovery period). Other food consumption values were similar to controls.

D. LIVER WEIGHT - At 800 ppm, absolute and relative to body liver weights were increased ($p \leq 0.05$) at Days 7 (↑26-28%) and 28 (↑25-27%; Table 2). Although liver weights in the 200 ppm group were slightly increased, the increases were not statistically significant ($p > 0.05$) and were comparable to historical controls. The liver weights at 40 ppm were similar to controls. After the recovery period, the liver weights of the treated animals were similar to controls.

Table 2. Mean (±SD) of liver weights in male mice treated with oxyfluorfen for 28 days. [a]

Parameter	Dose (ppm) 0	40	200	800	Historical Control Range [b]
Day 7					
Terminal body weight (g)	34.4±2.1	34.9±2.9	35.7±2.3	33.8±2.4	NR
Liver					
Absolute (g)	1.97±0.12	2.05±0.23	2.21±0.32	2.48±0.39* (↑26)	NR
Relative to body (%)	5.74±0.37	5.87±0.43	6.20±0.70	7.32±0.77* (↑28)	NR
Day 28					
Terminal body weight (g)	36.3±1.8	36.1±3.2	36.5±2.5	37.0±2.4	NR
Liver					
Absolute (g)	1.84±0.22	1.83±0.23	1.97±0.12	2.35±0.34* (↑27)	1.85-2.18
Relative to body (%)	5.07±0.43	5.06±0.38	5.39±0.22	6.33±0.65* (↑25)	5.48-6.29
Recovery					
Terminal body weight (g)	37.4±2.5	NT	NT	40.5±2.6* (↑8)	NR
Liver					
Absolute (g)	2.10±0.15	NT	NT	2.26±0.19	NR
Relative to body (%)	5.62±0.41	NT	NT	5.58±0.34	NR

a Data (n=10) were obtained from Table 8 on pages 51-52 of MRID 46373101. Percent difference from controls, calculated by the reviewers, is included in parentheses.

b Details (dates studies were conducted, number of animals, performing laboratory, etc.) concerning the historical controls, obtained from 4-week studies were not provided.

NR Not reported

NT Not tested

E. HEPATIC TISSUE EXAMINATION

1. S-phase DNA synthesis - The hepatocellular S-phase DNA synthesis labeling index values were very variable as shown by the large standard deviations.

At day 7, mean labeling index values for 40 and 200 ppm groups were similar to controls. With increased duration of treatment, at 200 ppm on Day 28, the labeling index (%) was increased (not statistically significant [NS]) in the centrilobular (↑143%), midzonal (↑73%), and periportal (↑75%) regions (Table 3). At 800 ppm, labeling index was increased at Days 7 (↑116-128%), 28 (↑778-1022%), and following recovery (↑20-105%) in each evaluated hepatic region. These increases were significant ($p \leq 0.05$) in the centrilobular region at all times, at Day 28 in all regions, and following recovery in the centrilobular and midzonal regions. Partial recovery was demonstrated. The labeling index was similar to controls at 40 ppm.

Table 3. Mean (±SD) labeling index (%) for hepatocellular S-phase DNA synthesis at selected intervals in male mice treated with oxyfluorfen for 28 days. [a]

Day	Dose (ppm)			
	0	40	200	800
Centrilobular				
7	1.49±1.24	0.88±0.56	0.84±0.61	3.40±2.41* (↑128)
28	1.43±1.22	1.47±1.75	3.47±1.40 (↑143)	14.91±7.25* (↑943)
Recovery Day 28 [b]	2.07±1.02	NT	NT	4.01±2.62* (↑94)
Midzonal				
7	1.20±1.27	0.73±0.35	0.81±0.75	2.70±2.44 (↑125)
28	1.54±1.55	1.22±0.98	2.66±1.19 (↑73)	13.52±5.93* (↑778)
Recovery Day 28 [b]	2.00±1.21	NT	NT	4.10±2.15* (↑105)
Periportal				
7	1.31±1.34	0.89±0.49	0.69±0.60	2.83±2.63 (↑116)
28	1.15±0.94	1.41±1.49	2.01±1.00 (↑75)	12.90±5.34* (↑1022)
Recovery Day 28 [b]	2.03±1.18	NT	NT	2.43±1.31 (↑20)

a Data (n=10) were obtained from Table 10 on pages 56-58 of MRID 46373101. Percent difference from controls, calculated by the reviewers, is included in parentheses.

b 10 males were treated for 28 days and then maintained on untreated diet for 28 days before being sacrificed.

NT Not tested

* Significantly different from controls; $p \leq 0.05$

2. <u>Electron microscopy and peroxisome quantitation</u> - Liver samples were reportedly adequate for a qualitative assessment of organelles. There was no evidence of an increase in number of peroxisomes at 800 ppm.

Non-membrane limited inclusions, consistent with lipid and the vacuolization noted with light microscopy were observed in all samples. The severity increased at 800 ppm (slight to moderate numbers, numerous, few) vs controls (rare). One mouse at 800 ppm had significant centrilobular hepatocellular degeneration consistent with necrosis and inflammation observed with light microscopy.

3.<u>Acyl-CoA oxidase assay</u> - Results were very variable as shown by the large standard deviations.

Specific activity (nm/min/mg protein) of ACO was increased ($p \leq 0.05$) by 395% at 800 ppm by Day 28 (Table 4). Only a minimal increase (NS) in ACO activity was noted at 200 ppm (↑55%), a tumorigenic dosage. ACO activity returned to control levels following the 28 day recovery period.

Table 4. Mean (±SD) of acyl-CoA oxidase activity (nm/min/mg protein) in male mice treated with oxyfluorfen for 28 days. [a]

Dose (ppm)			
0	**40**	**200**	**800**
Treatment Day 28			
8.02±2.93	8.96±4.03	12.47±8.17 (↑55)	39.76±14.48* (↑395)
Recovery			
6.40±3.08	NT	NT	7.48±6.57

a Data (n=10) were obtained from Table 9 on pages 54-55 of MRID 46373101. Percent difference from controls, calculated by the reviewers, is included in parentheses.

NT Not tested

4. Histologic examination - No treatment-related effect on the histology of the liver was evident following 7 days of treatment with oxyfluorfen at doses up to 800 ppm (Table 5). On Day 7 at 200 and 800 ppm, 1/10 animals had very slight multifocal centrilobular/midzonal hepatocyte mitotic alteration vs 0/10 controls.

On Day 28 at 200 and 800 ppm, increased incidences in the following histological lesions were observed (# affected/10 treated vs controls): slight centrilobular/midzonal hepatocyte hypertrophy (6-10/10 vs 3/10); and very slight to moderate centrilobular/midzonal hepatocyte vacuolization consistent with fatty change (5-10 vs 0/10; Table 5). On Day 28 at 800 ppm, these additional histological lesions were noted: (i) very slight to slight multifocal centrilobular/midzonal hepatocyte necrosis (9/10 vs 0/10); (ii) very slight multifocal subacute to chronic inflammation (6/10 vs 0/10); (iii) very slight multifocal hepatocyte karyomegaly (4/10 vs 0/10); (iv) very slight multifocal centrilobular/midzonal hepatocyte mitotic alteration (5/10 vs 0/10); and (v) very slight multifocal sinusoid centrilobular/midzonal pigment-laden macrophages (4/10 vs 0/10). Some of these changes (inflammation, karyomegaly, necrosis, and pigment-laden macrophages) were also seen in single animals at 200 ppm.

Following the recovery period, partial or complete recovery was observed for all findings except slight centrilobular/midzonal hepatocyte hypertrophy (10/10 treated vs 5/10 controls) and very slight multifocal hepatocyte karyomegaly (8/10 treated vs 0/10 controls) (Table 5). Recovery was demonstrated for these additional very slight grade findings where increased incidences were noted during treatment: multifocal centrilobular/midzonal hepatocyte mitotic alteration (2/10 vs 0/10); and multifocal centrilobular/midzonal hepatocyte necrosis (1/10 vs 0/10).

Table 5. Selected non-neoplastic hepatic histological findings (# affected/10) in male mice

Non-neoplastic hepatic lesion		Dose (ppm)			
		0	40	200	800
Day 7					
Hypertrophy, hepatocyte, centrilobular/midzonal	Total (slight)	1	0	0	0
Mitotic alteration, hepatocyte, centrilobular/midzonal, multifocal	Total (very slight)	0	0	1	1
Day 28					
Hypertrophy, hepatocyte, centrilobular/midzonal	Total (slight)	3	2	6	10
Vacuolization consistent with fatty change, hepatocyte, centrilobular/midzonal	Total very slight slight moderate	0 0 0 0	0 0 0 0	5 3 2 0	10 3 5 2
Necrosis, individual hepatocyte, centrilobular/midzonal, multifocal	Total very slight slight	0 0 0	0 0 0	1 1 0	9 6 3
Inflammation, subacute to chronic, multifocal	Total (very slight)	0	0	1	6
Karyomegaly, hepatocyte, multifocal	Total (very slight)	0	0	1	4
Mitotic alteration, hepatocyte, centrilobular/midzonal, multifocal	Total (very slight)	0	0	0	5
Pigment-laden macrophages, centrilobular/midzonal, sinusoid, multifocal	Total (very slight)	0	0	1	4
Recovery					
Hypertrophy, hepatocyte, centrilobular/midzonal	Total (slight)	5	NT	NT	10
Karyomegaly, hepatocyte, multifocal	Total (very slight)	0	NT	NT	8
Mitotic alteration, hepatocyte, centrilobular/midzonal, multifocal	Total (very slight)	0	NT	NT	2
Necrosis, individual hepatocyte, centrilobular/midzonal, focal	Total (very slight)	0	NT	NT	1
Necrosis, individual hepatocyte, centrilobular/midzonal, multifocal	Total (very slight)	0	NT	NT	1
Necrosis, inflammation, hepatocyte, focal	Total (very slight)	1	NT	NT	0

Data (n=10) from Table 11 on page 59-62 of MRID 46373101.
NT Not tested

III. DISCUSSION and CONCLUSIONS

A. <u>INVESTIGATORS' CONCLUSIONS</u> - It was concluded that the consumption of oxyfluorfen at 800 ppm resulted in a pattern of responses in liver suggesting a mixed mode of tumorigenic action. A mild induction of peroxisome enzyme activity was noted, but the primary response was degenerative changes in the liver which preceded a pronounced hepatocellular proliferation. The trend of increasing S-phase synthesis with increasing time of exposure is not characteristic of the transient mitogenic activity of most peroxisome proliferators and suggests a

secondary level of regenerative cell proliferation at 800 ppm. Most treatment-related changes appeared to be reversible following cessation of treatment.

B. REVIEWER COMMENTS -

The number of hepatic peroxisomes were not affected by treatment. There was an increase in acyl-CoA oxidase activity in the 800 ppm group on day 28 (395% of control) with activity returned to control values after a 28-day recovery period. The S-phase labeling index in the 800 ppm group was increased slightly on day 7 (approximately 125% in 3 liver regions), was increased to a greater extent on day 28 (approximately 1000% on day 28), and had returned nearly to control values after the recovery period (increased approximately 100% in 2 regions).

Absolute and relative liver weights were increased in the 800 ppm group on days 7 and 28 (increased approximately 25%) but were similar to control values after a 28-day recovery period.

No treatment-related effect on the histology of the liver was evident following 7 days of treatment in any of the dose groups. By Day 28, liver effects at 200 and 800 ppm included: (i) increased incidences of slight centrilobular/midzonal hepatocyte hypertrophy and (ii) very slight to moderate centrilobular/midzonal hepatocyte vacuolization consistent with fatty change. Other changes in the 800 ppm group on Day 28 included: (i) very slight to slight multifocal centrilobular/midzonal hepatocyte necrosis (9 vs 0); (ii) very slight subacute to chronic multifocal inflammation (6 vs 0); (iii) very slight multifocal hepatocyte karyomegaly (4 vs 0); (iv) very slight multifocal centrilobular/midzonal hepatocyte mitotic alteration (5 vs 0); and (v) very slight multifocal sinusoid centrilobular/midzonal pigment laden macrophages (4 vs 0). Some of these changes (inflammation, karyomegaly, necrosis, and pigment laden macrophages) were also seen in a single animal at 200 ppm. Persistent findings after the recovery period included slight centrilobular/midzonal hepatocyte hypertrophy (10/10 treated vs 5/10 controls) and very slight multifocal hepatocyte karyomegaly (8/10 treated vs 0/10 controls).

This study is classified **acceptable/non-guideline.**

C. STUDY DEFICIENCIES - No deficiencies were noted.

13544

R158482

Chemical: Oxyfluorfen

PC Code:
111601

HED File Code: 11000 Chemistry Reviews
Memo Date: 4/3/2008
File ID: TX0053039
Accession #: 000-00-0125

HED Records Reference Center
5/8/2008